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Smarter Health Care
National Research Programme

Déterminer de manière fiable la durée de la thérapie antibiotique

PIRATE PROJECT

The PIRATE PROJECT: a Point-of-care, Informatics-based Randomized, controlled trial for decreasing over-utilization of Antibiotic ThErapy in Gram-negative Bacteremia

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No conflicts of interest

Outline

- Finding the evidence to support a reduction in antimicrobial usage
  - Point-of-care (POC) randomization trials
    - Learning healthcare systems

- The PIRATE project
  - Antibiotic resistance & what we should learn from our patients
  - Randomization at the point of care for determining optimal antibiotic durations for Gram-negative bacteremia
  - Substudies

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When the drugs don't work

because we overused them

because we lacked evidence

to show that less usage is OK

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24 January 2013 Last updated at 13:18

Antibiotic 'apocalypse' warning

By James Gallagher
Health and science reporter, BBC News

The rise in drug resistant infections is comparable to the threat of global warming, according to the chief medical officer for England.

Prof Dame Sally Davies said bacteria were becoming resistant to current drugs and there were few antibiotics to replace them.

She told a committee of MPs that going for a routine operation could become deadly due to the threat of infection.

Drug resistance is a problem in tuberculosis

Experts said it was a global problem and needed much more attention.

Antibiotics have been one of the greatest success stories in medicine.

Related Stories

Warning on antibiotic resistance

Resistance to antibiotics now 'ticking timebomb'

'Catastrophic threat' warning from Government's Chief Medical Officer

'Even minor surgery may lead to death'

Call for tighter rein on GP prescriptions

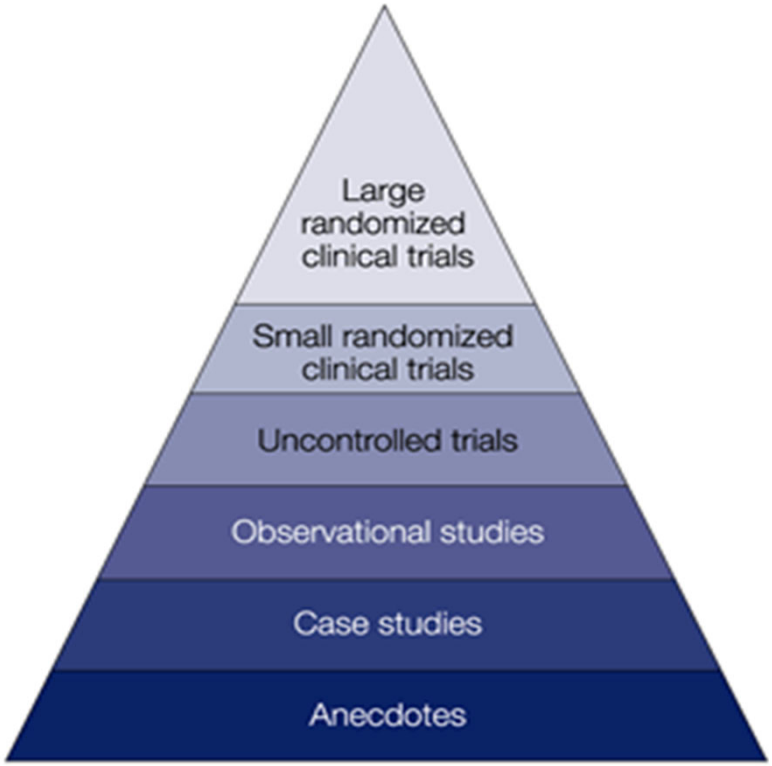
The Economist

When the drugs don't work

The rise of antibiotic resistance

Point-of-care randomization studies

- Hierarchy of evidence



Engel et al. *Nat Rev Drug Discov* 2002; 1(3): 229-37).

- We don't have enough randomized controlled trials in infectious diseases (only 16% of IDSA recommendations based on them)
- And even randomized controlled trials may lack external validity…
- Spontaneous randomizations occur daily in the clinic, but this "evidence" goes uncollected (anecdotes)

Khan et al. Clin Infect Dis 2010; 51(10): 1147-56

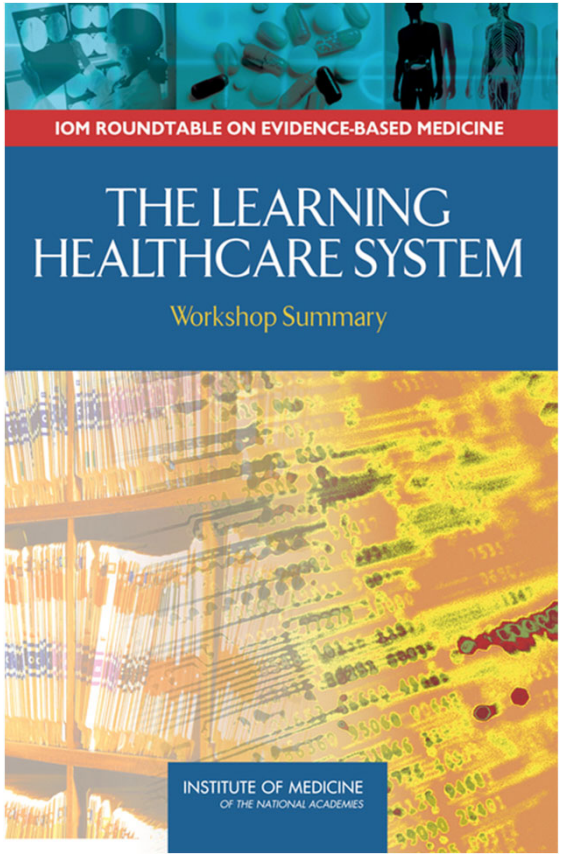
Point-of-care randomization studies

- Use the electronic health record (EHR) to structure spontaneous “pseudo-randomizations” at the point of care
- Enable the coherent study of patient outcomes
  - Data from “real” patients
  - Follow-up visits integrated into usual care
- Clinical evidence can come only from the clinic
- Only suitable for comparing **approved** treatments or diagnostic techniques toward which there is clinical equipoise

Learning healthcare systems

- Institute of Medicine (National Academy of Sciences), 2007 :

A learning healthcare system is…designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care.



Common Purpose principles of learning healthcare systems

1. Respect the rights and dignity of patients
2. Respect the clinical judgments of clinicians
3. Provide optimal care to each patient
4. Avoid imposing nonclinical risks and burdens on patients
5. Reduce health inequalities among populations
6. Conduct activities that foster learning from clinical care and clinical information
7. Contribute to the common purpose of improving the quality and value of clinical care and health care systems

Point-of-care randomization

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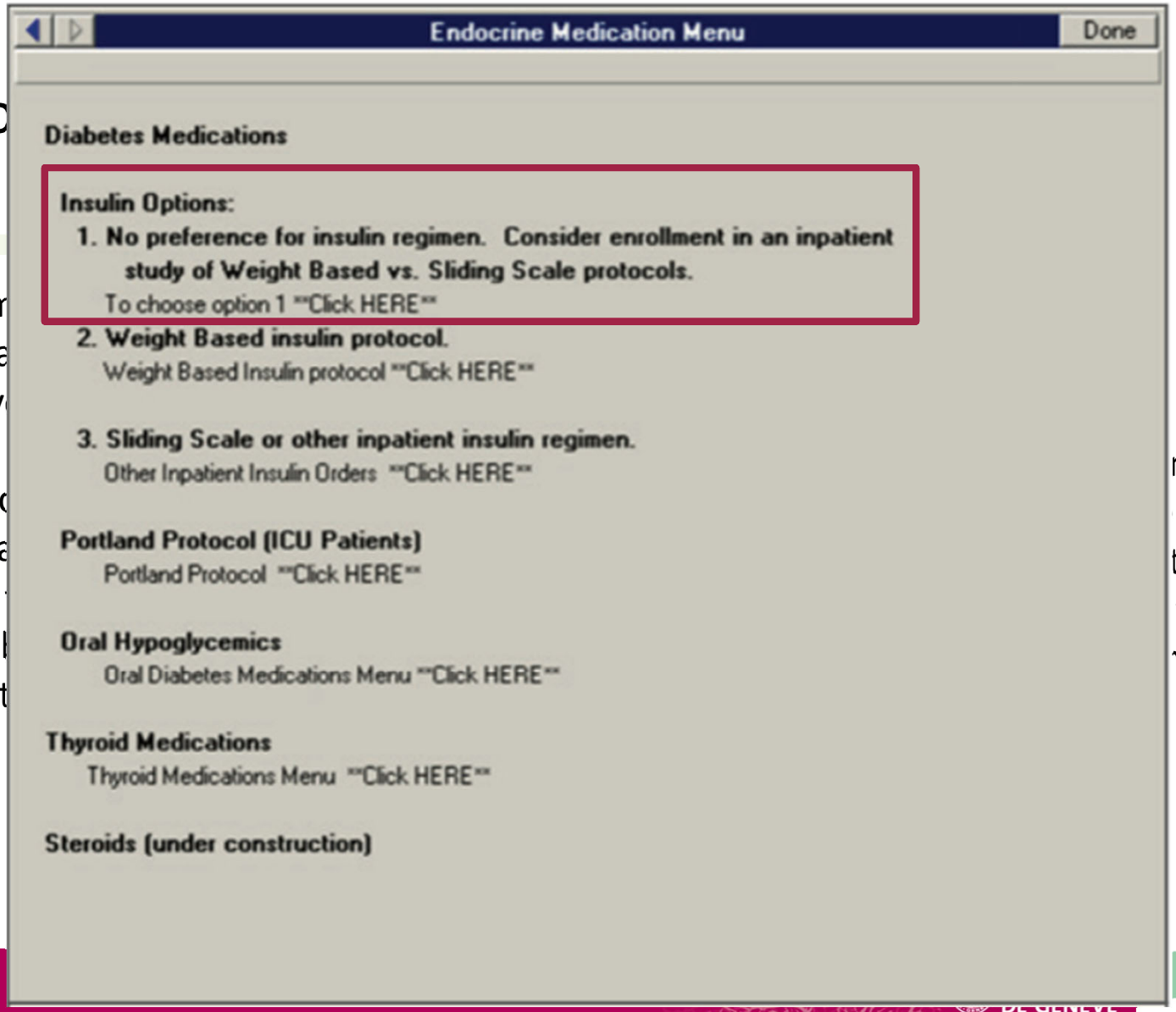

Establishing a point-of-care randomization platform in Switzerland

Box 2
Hypothetical examples of point-of-care trials in infectious disease

- Duration studies: optimal duration of antibiotic therapy for (a) community-acquired pneumonia, (b) uncomplicated pyelonephritis, (c) Gram-negative bacteraemia; early switch to oral antibiotic therapy; etc.
- Antibiotic choice studies: linezolid vs. vancomycin for skin and soft tissue infections; fosfomycin vs. ciprofloxacin for prophylaxis before transrectal prostate biopsy; cloxacillin vs. cefazolin for MSSA bacteraemia; combination vs. monotherapy for carbapenem-resistant, Gram-negative infections; β-lactam monotherapy vs. β-lactam/aminoglycoside for *Pseudomonas aeruginosa* bacteraemia; etc.
- Dosing and schedule: meropenem 1 g three times a day vs. 2 g three times a day; intermittent vs. continuous infusion of antibiotics; pharmacokinetic studies in which no more than routine blood sampling is needed; etc.

MSSA, methicillin-susceptible *Staphylococcus aureus*.

Huttner A, Leibovici L et al. Closing the evidence gap in infectious disease: point-of-care randomization and informed consent. Clin Microbiol Inf 2016

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Establishing a point-of-care randomization platform in Switzerland

- Help from above

FNSNF Swiss National Science Foundation

74 NRP Smarter Health Care National Research Programme

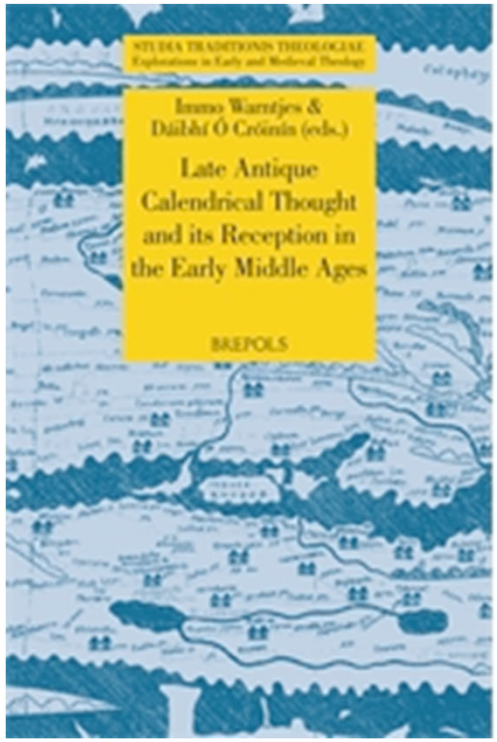
- A convincing & “easy” first test case, with plenty of safety valves…

The PIRATE project: a Point-of-care, Informatics-based Randomised, controlled trial for decreasing over-utilisation of Antibiotic Therapy in Elderly and comorbid populations

Study question of the platform’s prototype trial:
Are shorter antibiotic courses non-inferior to 14 day courses for Gram-negative bacteremia?

Rationale for the PIRATE project

- We know we overuse antibiotics
- We know that this overuse leaves patients with resistant organisms
- Antibiotic durations are arbitrary…and lunar!
- But physicians are generally afraid to shorten durations without solid (randomized) evidence



Holmes AH et al. *Lancet.* 2015; Bell BG et al. *BMC Infect Dis.* 2014;14:13;
Zarkotou O et al. *Clin Microbiol Infect.* 2011;17(12):1798-1803.

Are shorter antibiotic courses non-inferior to 14 day courses for Gram-negative bacteremia?

- **Gram-negative bacteremia is on the rise**
  - Patients are getting older, more co-morbid, and more immunosuppressed
- No RCT evaluating the optimal duration of therapy for Gram-negative bacteremia (GNB) published
- Some physicians give 14 days of antibiotics, some 7…and some even only 5 (“pseudo-randomizations”)
- Indirect evidence that, in patients without structural complications who are improving, shorter durations are safe

Havey TC, Fowler RA, Daneman N. *Crit Care.* 2011;15(6):R267; Sandberg T, Skoog G, Hermansson AB, et al. *Lancet.* 2012;380(9840):484-490; Chastre J, Wolff M, Fagon JY, et al. *JAMA.* 2003;290(19):2588-2598

Rationale for the PIRATE project

- So why not structure these pseudo-randomizations at the point of care and follow our patients' clinical outcomes?

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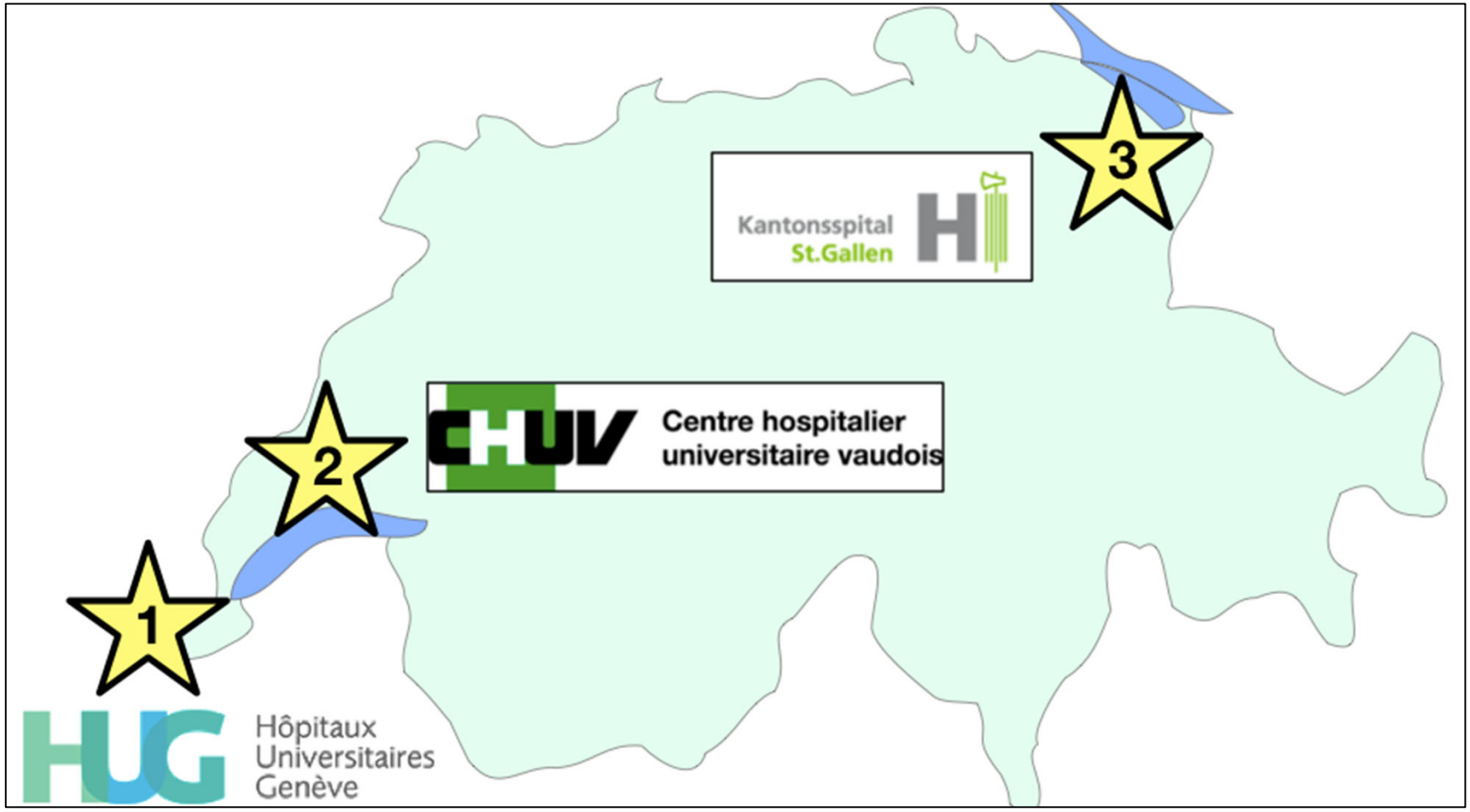
The PIRATE trial's sites…



PIRATE PROJECT

… and team

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Kantonsspital St.Gallen

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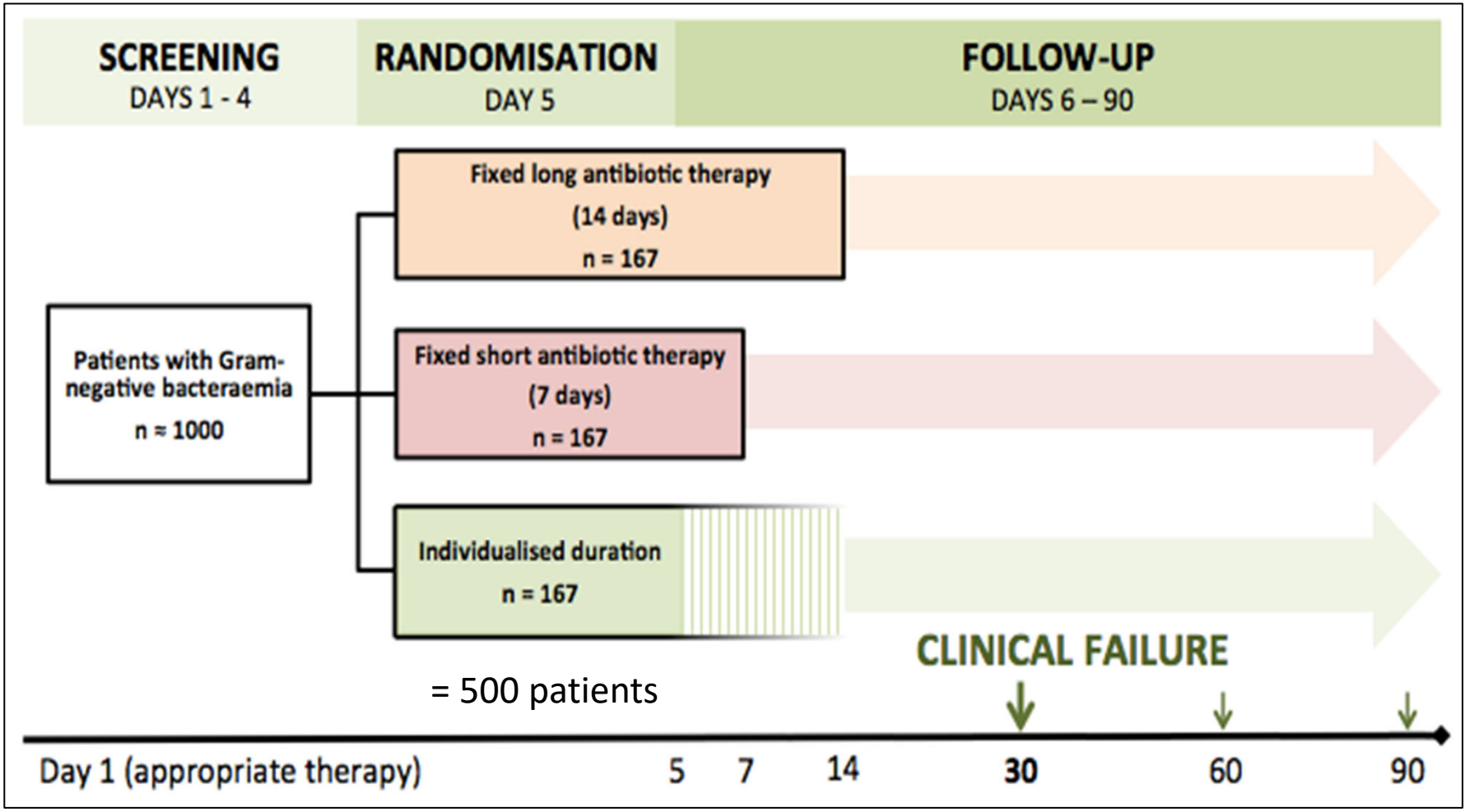
Study design

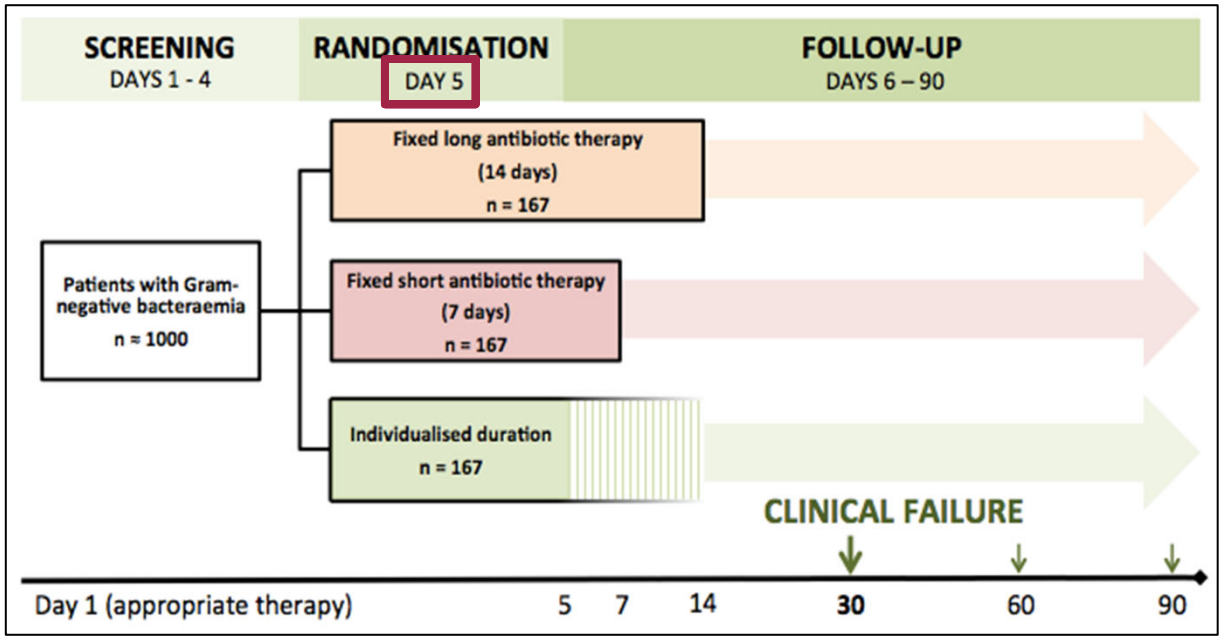
Randomized (1:1:1) controlled, triple-blind phase IV POC trial



Designated investigators & patients blinded until antibiotic discontinuation

Analyst blinded

Population, outcomes



Primary outcome = clinical failure = at least one of the following:

Inclusion criteria:

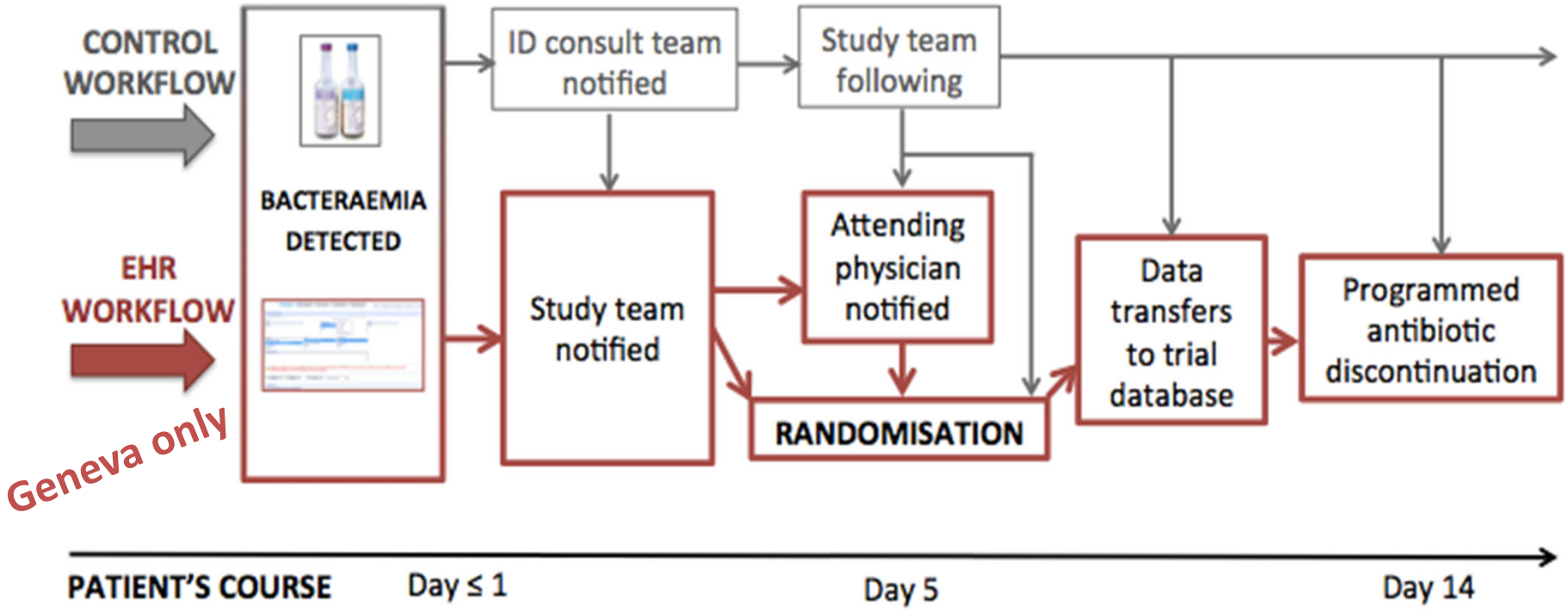
1. Age ≥ 18 years
2. The presence of Gram-negative bacteria in at least one blood culture bottle
3. Treatment with a microbiologically efficacious antibiotic

Exclusion criteria:

1. Immunosuppression
2. Abscess/ other complications
3. Certain “difficult” organisms
4. Etc….

- **Relapse**: a recurrent bacteremia due to the same bacterium occurring from the day of treatment cessation through day 30
- **Local suppurative complication** not present at infection onset
- **Distant complications** of the initial infection, defined by growth of the same bacterium causing the initial bacteremia (as determined by antibiotic susceptibility profiling)
- **The restarting of Gram-negative-directed antibiotic therapy** due to clinical worsening suspected to be due to the initial infecting organism and for which there is no alternate diagnosis/pathogen suspected
- **Death** due to any cause through day 30

Study design: informatics component



Electronic-healthcare record workflow for patient identification, randomization and follow-up. The EHR workflow is outlined in red, the control ("back-up") workflow in grey. Grey arrows indicate safety valves; these cover all points at which the EHR workflow could malfunction. In this hypothetical case, the patient has been randomized to the control arm (antibiotic therapy duration of 14 days).

Informatics component

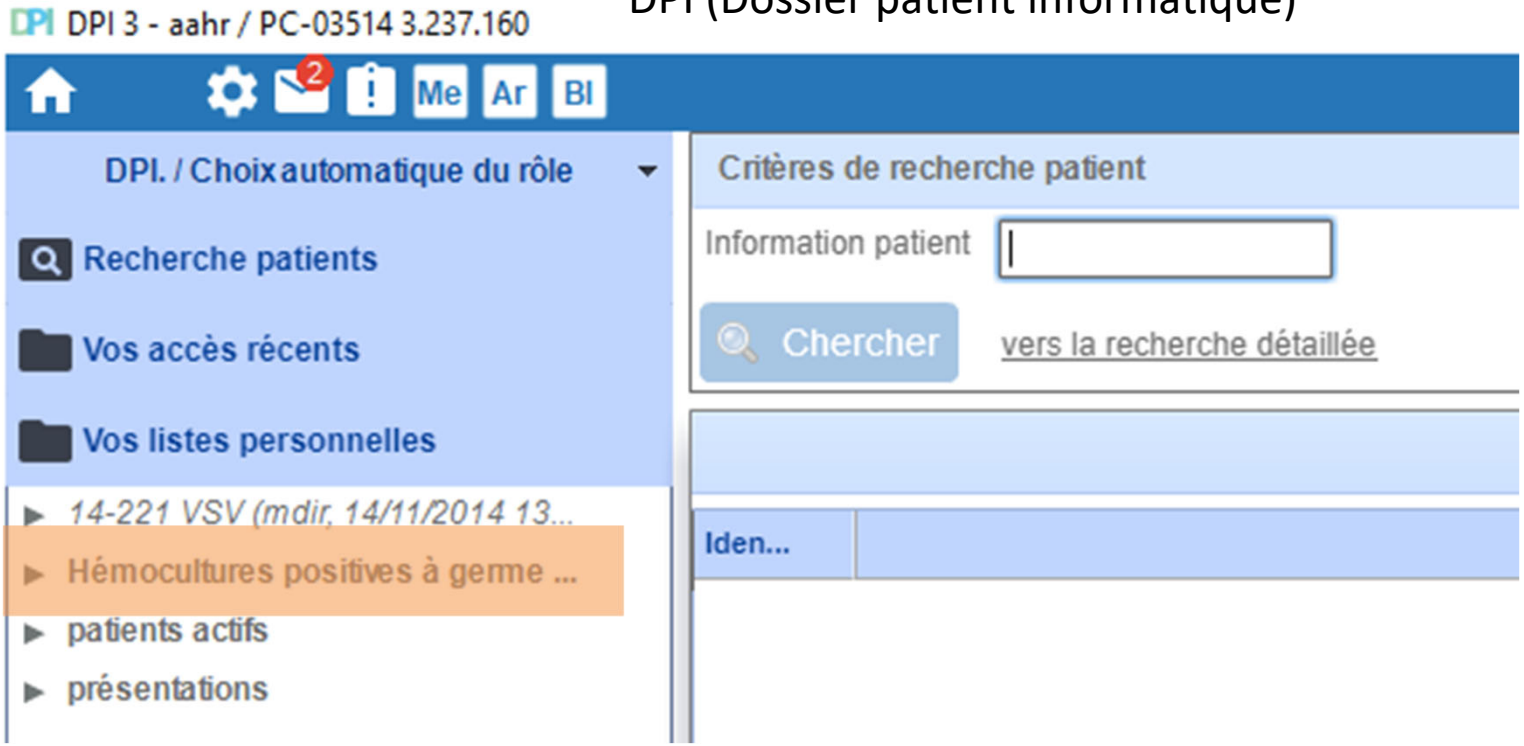
SecuTrial (study database)

DPI (Dossier Patient Intégré)
Electronic health record

SecuTrial (study database)

Automated case finding through the electronic health record

DPI (Dossier patient informatique)



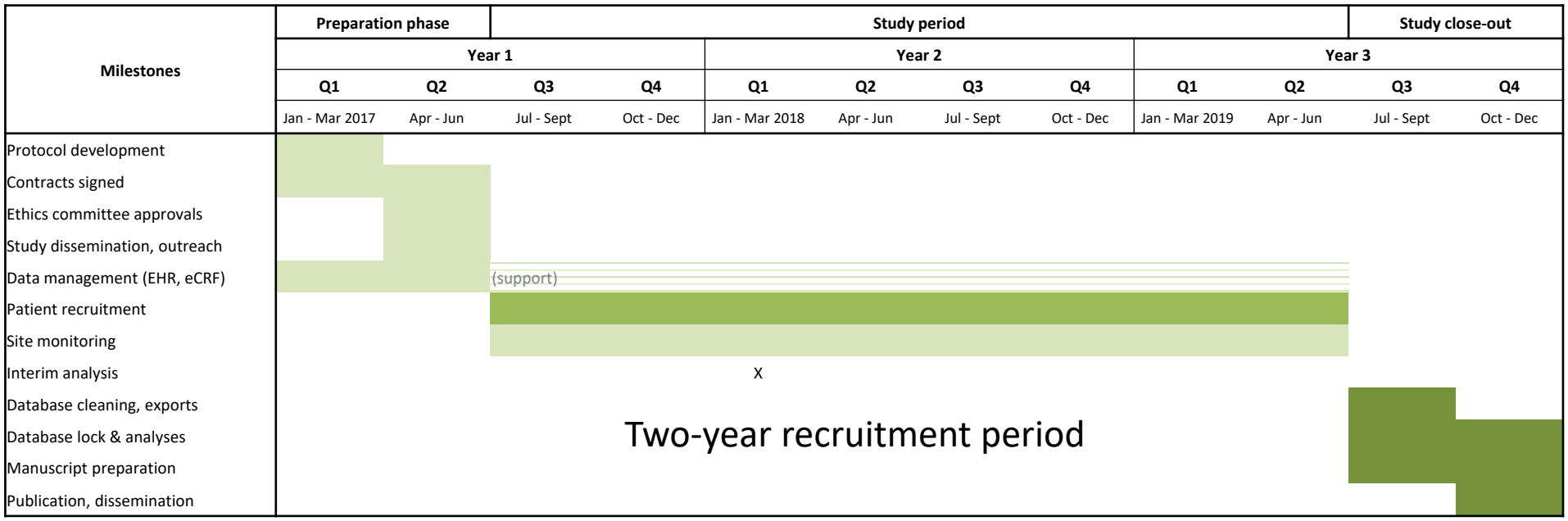
Study schedule (keeping it simple)

Study visit/observation point	1	2	3	4	5	6	7
	Screening	Randomization	Follow-up				
Timeline (days)	**0-4**	**5**	**8**	**12**	**30**	**60**	**90**
Window period (days)			±2	±2	±7	±14	±21
Informed consent	X	(X)			(X)	(X)	(X)
Entry criteria	X						
CRP measurement* (2ml blood)			(X)	(X)			
AEs reviewed					X		
SAEs reviewed					X	X	X
Other outcomes data collected					X	X	X

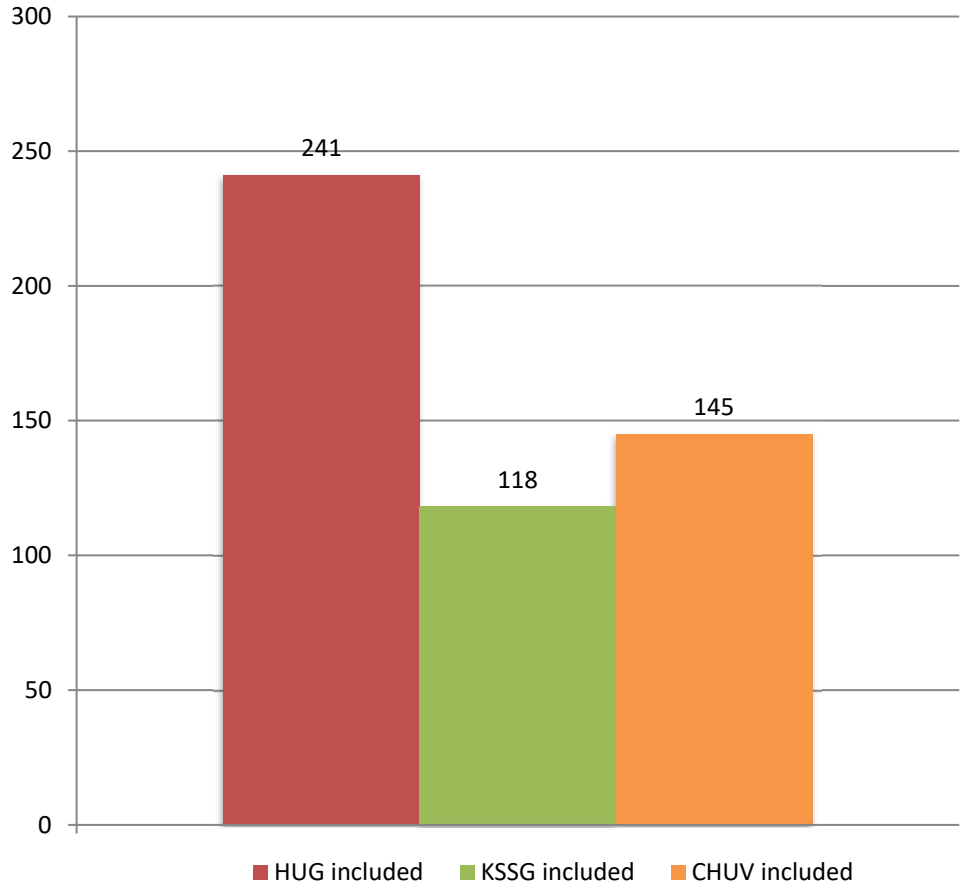
Study timeline

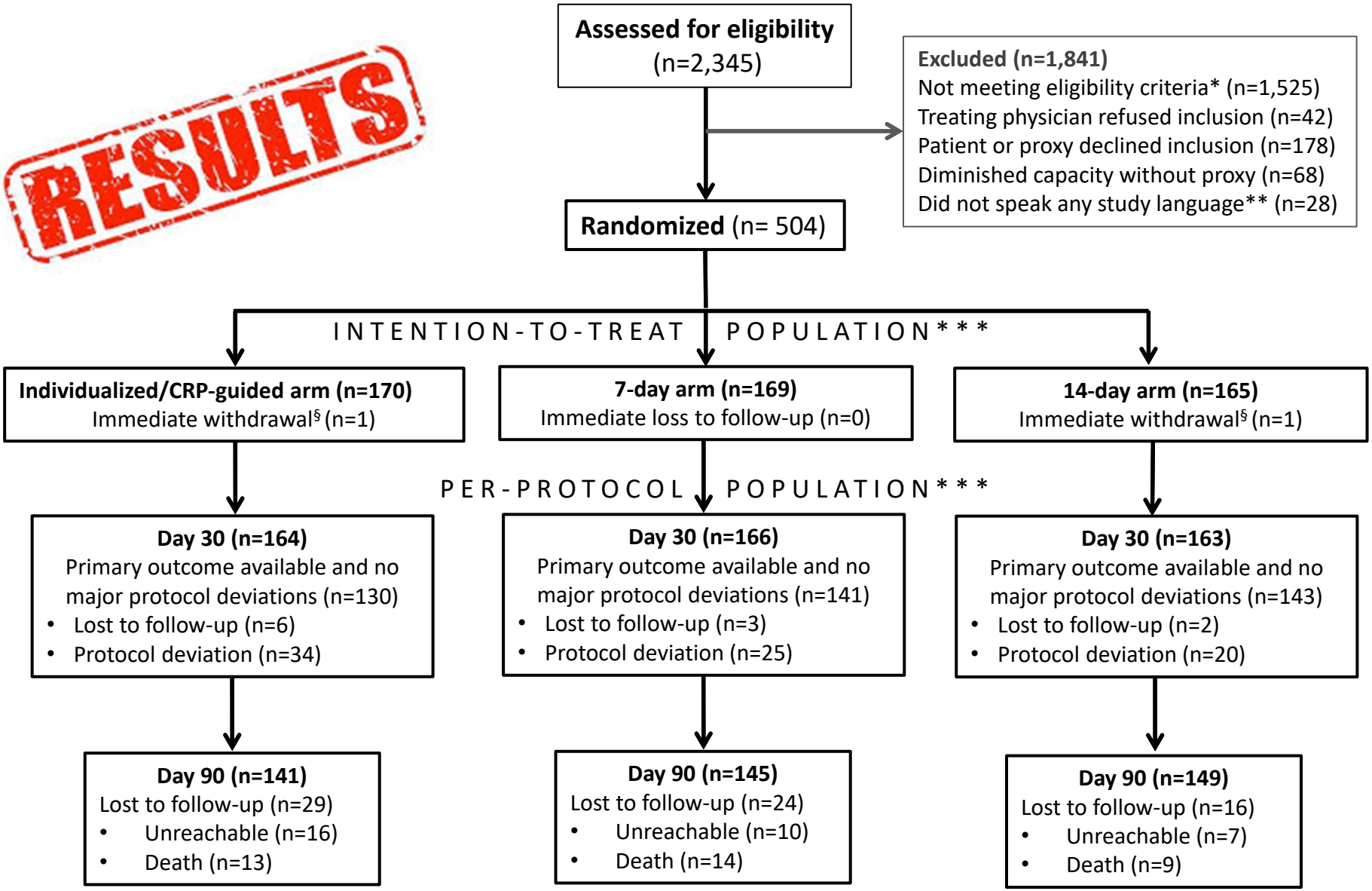
Geneva launch
1 April 2017

Lausanne &
St. Gallen launch
1 May 2017



Recruitment target reached in May 2019





*Reasons for exclusion: complicated infection (n=739); immunosuppression (n=392); excluded bacteria (n=388); fever in the preceding 24h (n=67); hemodynamic instability in the preceding 24h (n=30); bacteremia in the previous 60 days (n=13)

** Informed consent documents were available in German, French and English.

***Both ITT and PP populations were analyzed. Data on the primary outcome were missing for 11/504 (2%) patients randomized.

§No antibiotic-duration data available.

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RESULTS

- Intention-to-treat and per-protocol analyses for the main outcomes are complete

- Nested studies
  - PIRATE RESISTANCE
    - Metagenomic analysis of the effects of antibiotic durations on the intestinal microbiome
  - EPCO
    - Excluded Patients' Clinical Outcomes
  - Etc.

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RESULTS

- Results will be presented at the European Congress on Clinical Microbiology and Infectious Diseases (April 2020)

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Thank you

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